REMARKS

Claims 1 to 7, 13, and 15 to 21 are pending in this application and are rejected. Applicants are herein amending claim 1. Applicants request reconsideration in light of the amendments to the claims and accompanying remarks.

Summary of Rejections

Claims 1 to 7, 13, and 15 to 21 ***stand*** rejected as follows:

- as allegedly not enabled for the prevention of vasomotor symptoms under 35 U.S.C. § 112, first paragraph; and
- as allegedly obvious over WO 98/36744 (Briley application) in view of US 2003/0216366 (Leonard application) under 35 U.S.C. § 103(a).

Claims 1 to 7, 13, and 15 to 21 are ***newly*** rejected as follows:

- as allegedly not enabled for the use of milnacipran in the treatment of vasomotor symptoms under 35 U.S.C. § 112, first paragraph; and
- as provisionally rejected on the grounds of nonstatutory obviousness-type double patenting over claims 7, 9, 10, and 13 to 19 of copending U.S. Application No. 10/685,974 in view of Berendsen (2000).

Amendments to Claims

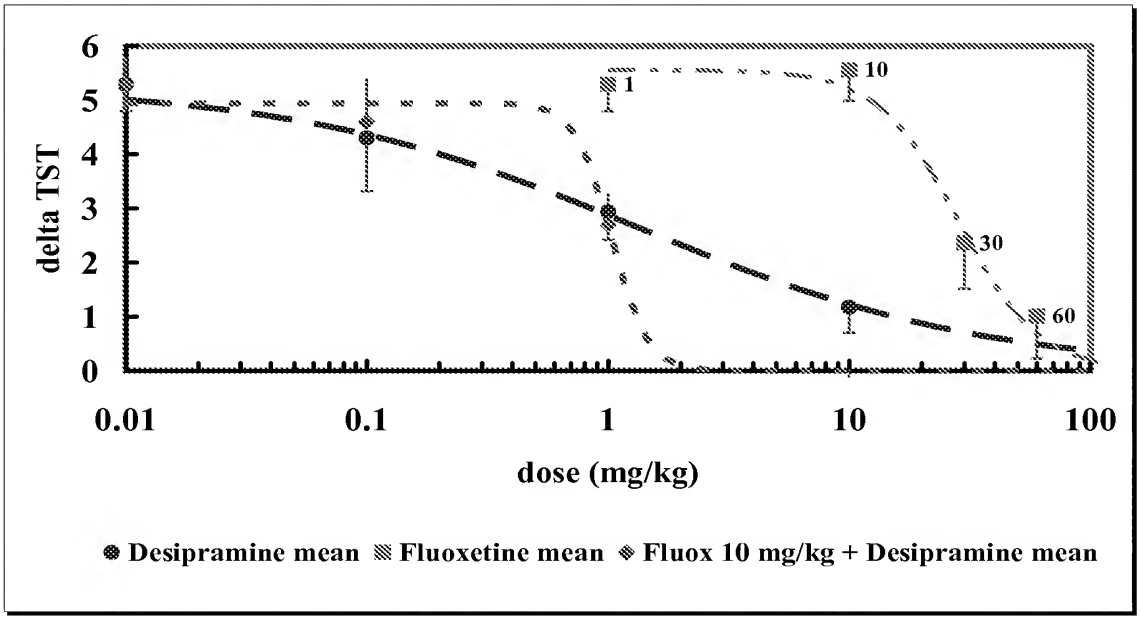
Applicants are herein amending claim 1 to further clarify that the vasomotor symptoms are selected from the group consisting of hot flushes, excessive perspiration, night sweats, and combinations thereof. No new matter is introduced by the amendment to claim 1. Support for the amendment may be found in paragraph **[0057]** of the specification.

Rejections under 35 U.S.C. § 112, first paragraph

Prevention of Vasomotor Symptoms

Claims 1 to 7, 13, and 15 to 21 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled for the prevention of vasomotor symptoms. Applicants respectfully traverse the rejection because not only does the use of milnacipran treats vasomotor symptoms, it also prevents vasomotor symptoms.

Milnacipran is a dual NRI/SRI compound. As explained in the specification in paragraph **[0042]**, an increasing dose of NRI and a 10 mg/kg dose of SRI were co-administered, hot flush was abated by **100%** at a 3 mg/kg dose of an NRI (desipramine) (as shown in **Figure 4**) compared with the 10 mg/kg dose (emphasis added). Thus, supporting the prevention as well as treatment of vasomotor symptoms.



Therefore, applicants submit that claims 1 to 7, 13, and 15 to 21 are enabled. However, in an effort to solely expedite prosecution, applicants are herein amending claim 1 to delete "or prevent," thereby rendering moot the enablement rejection of the claims. Accordingly,

applicants request withdrawal of the rejection of claims 1 to 7, 13, and 15 to 21 under 35 U.S.C. § 112, first paragraph.

Enablement of Milnacipran

Claims 1 to 7, 13, and 15 to 21 are newly rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled for the use of milnacipran in the treatment of vasomotor symptoms. Applicants respectfully traverse the rejection.

It is also our understanding the Examiner is requiring working examples for milnacipran to support the claims. We have provided actual working examples for other compounds (venlafaxine and O-DVS) having dual NRI/SRI activity to establish that such compounds may be used in low levels, *i.e.,* less than about 37.5 mg/day, to treat vasomotor symptoms. See Example 3. The applicants are confident, based on the results of the venlafaxine and O-DVS, that the milnacipran will be useful at low levels in the treatment of vasomotor symptoms. The Examiner points to the Spencer & Wilde reference at page 421 to show that milnacipran actually causes hot flushes. However, applicants wish to point out the dosage of the milnacipran in these tests was "usually at 100 or 200 mg/day" (page 420), which is considerably higher than the dosage limitation (37.5 mg/day) of the present claims. No evidence has been presented which casts doubt that the much lower dosages in the claims do not, in fact, abate hot flushes. Furthermore, NRI compounds in combination with SRI compounds surprisingly results in such benefits as clearer dose-related definitions of efficacy, diminished reported side effect, superior therapy due to synergistic activity, and accordingly, an improved therapeutic index. For example, high doses of NRIs or NRI/SRI compounds alone can induce vomiting, nausea, sweating, and flushes (Janowsky, *et al., Journal of Clinical Psychiatry*, **1984**, 45(10 Pt 2): 3-9)(cited as Reference No. 15 in Information Disclosure Statement). Accordingly, it is clear that while NRI compounds administered at high doses can cause hot flushes, they may be used at lower dosages to treat the same condition. Likewise, while NRI/SRI compounds at high doses can cause hot flushes, they

may be used at lower dosages to treat the condition, as shown in working Example 3 for venlafaxine and O-DVS.

Therefore, applicants submit that claims are enabled and request withdrawal of the rejection of claims 1 to 7, 13, and 15 to 21 under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 103(a)

Claims 1 to 7, 13, and 15 to 21 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over the Briley application in view of the Leonard application. Applicants respectfully traverse the rejection because the combination of references does not disclose, teach, or suggest the use of milnacipran for treating vasomotor symptoms, especially where the dosage level is low.

More specifically, the Office asserts that the Briley application discloses the use of milnacipran for treating sleeplessness but fails to disclose the levels required by the present claims. The Office looks to the Leonard application to establish that insomnia is a vasomotor symptom. The Office further argues that it would have been obvious to a skilled artisan to optimize the dosage level of milnacipran to reach the levels required by the present claims. Applicants submit that this logic if flawed for the following reasons.

The Briley application discloses that milnacipran is useful for treating certain psychiatric disorder, including, *inter alia,* sleeplessness. Claim 1 is directed to a method for treating vasomotor symptoms by administering milnacipran in an amount less than about 37.5 mg/day. Vasomotor symptoms are defined in the specification as follows:

> **[0001]** The phrases "vasomotor symptoms," "vasomotor instability symptoms" and "vasomotor disturbances" include, but are not limited to, hot flushes (flashes), insomnia, sleep disturbances, mood disorders, irritability, excessive perspiration, night sweats, fatigue, and the like, caused by, *inter alia*, thermoregulatory dysfunction.

> **[0002]** The term "hot flush" is an art-recognized term that refers to an episodic disturbance in body temperature typically consisting of a sudden skin flushing, usually accompanied by perspiration in a subject. The term "hot flush" may be used interchangeably with the terms vasomotor symptoms, vasomotor instability, vasomotor dysfunction, night sweats, vasomotor disturbances, and hot flash.

Applicants submit that the sleepnessness disclosed by the Briley application is not insomnia or a sleep disturbance associated with vasomotor symptoms, as defined in the specification. The title and abstract of Briley, the only English portions of the document, are silent with respect to any further details about the subjects suffering the sleeplessness. The clinical studies that appear to be described in the document do not appear to indicate the age or condition of the patients studied. In fact, the references teaches away from treating menopausal females and andropausal males, because at least some of the patients in the clinical studies are suffering from pre-menstrual dysphoria. However, to further clarify the terminology, applicants are herein amending claim 1 to explicitly specify that the vasomotor symptoms are caused by thermoregulatory dysfunction.

Applicants also disagree that it would have been obvious to the skilled artisan to optimize the level of milnacipran to reach applicants' claimed amount of less than about 37.5 mg/day. In fact, the state of the art actually taught away from lowering the maximum level of milnacipran, an NRI/SRI, as explained in the specification in paragraph **[0032]**:

> **[0003]** In one embodiment, it was discovered that using NRI compounds at low doses, below doses commonly used for antidepressant efficacy, results in an improved treatment to maintain normal thermoregulatory homeostasis. Furthermore, NRI compounds in combination with SRI compounds surprisingly results in such benefits as clearer dose-related definitions of efficacy, diminished reported side effect, superior therapy due to synergistic activity, and accordingly, an improved therapeutic index. For example, high doses of NRIs or NRI/SRI compounds alone can induce vomiting, nausea, sweating, and flushes (Janowsky, *et al., Journal of Clinical Psychiatry*, **1984**, 45(10 Pt 2): 3-9). The present invention provides treatment or prevention of vasomotor symptoms without side effects caused by using NRI alone at high doses.

Accordingly, applicants submit that claims 1 to 7, 13, and 15 to 21 are not obvious over the Briley application in view of the Leonard application and request withdrawal of the rejection of claims 1 to 7, 13, and 15 to 21 under 35 U.S.C. § 103(a).

Obviousness-type Double Patenting Rejections

Claims 1 to 7, 13, and 15 to 21 are newly and provisionally rejected on the grounds of nonstatutory obviousness-type double patenting over claims 7, 9, 10, and 13 to 19 of copending U.S. Application No. 10/685,974 in view of Berendsen (2000). Applicants request that this rejection be held in abeyance until the identification of otherwise allowable subject matter.

Conclusions

Applicants request:

- entry of the claim amendments;
- reconsideration and withdrawal of the enablement and obviousness rejections; and
- allowance of claims 1 to 7, 13, and 15 to 21.

If the Examiner is of a contrary view, the Examiner is requested to contact the undersigned attorney at (404) 459-5642.

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